*American Journal of Public Health*



# Editorials

## Editorial: Epidemiologic Data in Risk Assessment—Imperfect but Valuable

The first known human carcinogens were identified through prototypical epidemiologic studies: for example, the classic report by Percival Pott in 1775 on scrotal cancer among chimney sweeps from exposure to soot. However, as risk assessment approaches evolved in the latter half of this century, it became apparent that animal studies had the advantages of a randomized design, the administration of high doses so that a few hundred animals would suffice, and the potential to obtain an answer in 2–3 years rather than perhaps 20–30 years for the epidemiologic study. Therefore, a large body of animal carcinogenicity studies was created, and numerous methods were developed to analyze and project risk from the animal data.

Epidemiology has been late in coming to the risk assessment scene in any significant way for several reasons: (1) relatively few potential carcinogens had been studied epidemiologically before about 1975; (2) historically, much of occupational epidemiology was marginal as a risk assessment tool, largely because the assessment of exposure was lacking or limited; and (3) the risk assessment community had not come to appreciate fully the inadequacies of rodent-based risk assessment, one of several issues that Dr Hertz-Picciotto summarizes in this issue's Public Health Policy Forum.[1]

The single greatest weakness of epidemiologic risk assessment is that individual quantitative exposure information is very often limited or missing in occupational and environmental studies. The development of methods for retrospective exposure assessment is becoming an active area of research,[2] although at this point there appear to be various approaches to retrospective exposure assessment but little comparative evidence on the best approach(es). Unfortunately, a thorough retrospective exposure assessment is an expensive undertaking and may often increase the cost of an epidemiologic study severalfold. On the other hand, a good retrospective exposure assessment will increase the sensitivity and precision of the study because a dose–response analysis with reasonably accurate dose data has more statistical power than a cruder analysis.[3] The quantitative precision can also serve to rule out large risks that may have been imputed from animal data.[4,5] The epidemiologic community needs to communicate to corporate medical and managerial personnel the importance of supporting epidemiologic studies with sound retrospective exposure assessment, so that they will increasingly become active participants in developing such studies.

The risk assessment community has been moving away from a "positive evidence" approach (e.g., one positive study outweighs five negative ones) to a "weight of evidence" approach in which the information from all good-quality studies—mechanistic, experimental, and epidemiologic—is factored in when arriving at a judgment regarding carcinogenicity. This trend parallels the transformation that has occurred in epidemiology: study results are no longer thought of in a strict hypothesis-testing mode; rather, the results are seen as helping to solve an estimation problem—measuring the magnitude of risk with as much precision and validity as possible.[6] Thinking of quantita-

**Editor's Note.** See related articles by Hertz-Picciotto (p 484) and Wartenberg and Simon (p 491) in this issue's Public Health Policy Forum.

tive risk assessment as an *estimation* problem also makes room for incorporating nonpositive evidence (i.e., null results or results in the negative direction). However, nonpositive human evidence is meaningful only when it relates to prolonged and heavy exposure of a substantial number of persons and when the period of observation is long enough for a cancer excess to have appeared.[7]

In an accompanying commentary, Wartenberg and Simon have warned against employing negative studies in risk assessment because of the frequent insensitivity (i.e., low statistical power) of the studies.[8] However, it does not necessarily follow that positive studies with low expected statistical power are more credible than negative ones, since positive results in such studies are apt to be due to chance and to yield risk estimates that are severely inflated.[9]

Epidemiologic results, whether positive or nonpositive, are valuable largely to the extent that they are unbiased and *informative*. Informativeness implies that the results set relatively narrow bounds on the estimate of risk per unit dose. To achieve informativeness, the study or aggregate of studies must be large enough to have a fairly narrow confidence interval on the relative risk, *and* the dose levels must be high enough so that the confidence interval on the resultant risk estimate per unit dose is also small.

A low-dose study is unlikely to be very informative in the sense used here, because the small dose range means it will almost inevitably have a relatively wide confidence interval per unit dose. Furthermore, when the study dose level is low so that the risk estimate is close to unity, it is likely that the magnitude of bias associated with unmeasured variables in an observational study will equal or exceed the "true" risk, so that objectively one can have little confidence that the result is not attributable to masking or accentuation by unmeasured confounding variables. Hence, great care must be taken in using low-dose studies in risk assessment. Major problems of unmeasured confounding also afflict ecologic or correlational studies of environmental risks[10,11] and limit their value in risk assessment.

Even with occupational cohort studies, which usually generate the strongest epidemiologic data for risk assessors, there are often subtle unresolved issues of confounding. Confounding with regard to smoking or alcohol is often problematic, because historic individual data on these habits are seldom available. Alternate workplace exposures represent another potential source of confounding often overlooked in occupational studies. Some studies show that alternate exposures probably accounted for the putative association with the exposure under study.[12,13] Perhaps the most subtle type of confounding in occupational studies pertains to the healthy-worker survivor effect.[14] In essence, sick people have a relatively high risk of death and also are likely to terminate employment, so employment status is a time-dependent predictor of both the amount of exposure and the risk of death. Therefore, it functions as both an intermediate variable and a confounding variable, and ordinary exposure–response analyses yield biased estimates of the exposure effect, although statistical methods to resolve this bias are evolving.[15]

Epidemiologic data are uniquely suited to estimating the temporal pattern of risks. Quantitative risk assessments by government agencies, based on either animal or human data, have tended to extrapolate risks to older ages by assuming, in effect, a constant relative risk model. Because spontaneous rates of most cancers increase rapidly with age, this assumption projects a large risk at older ages. In contrast, detailed analyses of the temporal course of risk have shown for several major human carcinogens that the relative risks begin to decline within a few decades after exposure ceases.[16–20] Hence, the appropriate use of epidemiologic data has the potential to refine the temporal projection of risks, something that could not very well be done from animal data.

The commentary by Hertz-Picciotto[1] deals primarily with the quality and use of individual studies in risk assessment. The issues she addresses are essential because sound individual studies are the building blocks of risk assessment. However, in many cases risk assessment is fundamentally a process of using multiple studies to arrive at a judgment concerning probable causality and an estimate of the magnitude of risk, if any. In the case of epidemiologic data, an increasingly common way of deriving a central estimate of risk is through joint analyses of several studies (either meta-analysis based on summary risk estimates from the studies or pooled analysis based on the raw data), which provide an explicit statistical scheme for weighting studies according to their informativeness and for evaluating whether they are heterogeneous in their risk estimates.

Dealing with heterogeneity and factoring indices of study quality into the weighting scheme for a joint analysis are still primitive arts, as recent commentaries highlight.[21–24] However, these problems are not unique to epidemiologic meta-analysis; they also plague more informal, qualitative approaches to risk assessment, whether based on epidemiologic or experimental data, although with informal approaches the problems may not be highlighted as clearly as they are when joint analyses are performed. Nevertheless, it is clear that the finished product of a thoughtful and informed joint analysis is desirable for a weight of evidence risk assessment and that the process of systematically sorting through the quality of the relevant studies can be illuminating to the risk assessors.

Although many of the above points have been critical of epidemiologic practice and data, the hope is to stimulate informed approaches to producing high-quality epidemiologic data, which will increasingly play a central role in risk assessment. □

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# Editorial: Agent Orange in Vietnam

Few issues manifest the ideological divisions in our society as powerfully as the Vietnam War, and no public health issue is more entangled with our unease about that war than the health effects of dioxin. While the war and the dissension at home were still raging, Bertrand Russell charged that the US military was using carcinogenic herbicides in Vietnam. US newspapers responded with editorials stating that the eminent mathematician may be suffering from senility. Ironically, Admiral Zumwalt (who gave the order to use herbicides for tactical purposes in Vietnam) reportedly has come to believe that his son's early death from lymphoma was due to herbicide exposure in Vietnam. He nevertheless defends his decision as appropriate, given the American lives presumed saved by defoliation.

It may be because enough time has transpired since the war, and because our understanding of the relation between economic activity and environmental protection has sufficiently progressed, that we can approach the issue of the health effects of dioxin with some objectivity—even among the Vietnamese. Fortunately, our efforts in this regard can be informed by a much more substantial body of evidence than earlier efforts. The ideological nature of earlier evaluations was fueled, at least in part, by the scarcity of toxicologic and epidemiologic data directly relevant to the issue.

A report in this issue of the Journal[1] provides some new data in this regard. These data come from a group of scientists who have struggled for many years, usually without adequate funding, to measure dioxin levels in breast milk, adipose tissue, and blood from Vietnamese. Although these data are not from a systematic epidemiologic design—there may be problems with the representativeness of the samples selected, potential problems with the handling of samples, and so on—outright fraud would be necessary to artifactually produce the clear difference reported between persons residing in unsprayed (northern) and sprayed (southern and central) areas of Vietnam. The mean 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) blood level is 6 times greater in the southern/central group than in the northern. This large discrepancy is not found for other specific congeners of the higher chlorinated dioxins or furans, although the other congeners are generally higher in concentration in the sprayed areas. Since TCDD was the major dioxin-like contaminant in Agent Orange (a mixture of 2,4,5-trichlorophenoxyacetic acid [2,4,5-T] and 2,4-dichlorophenoxyacetic acid [2,4-D]), these findings suggest that the TCDD in 2,4,5-T may have found its way into the food chain of some Vietnamese. The elevated levels fron 1984 to 1992 may reflect much higher body burdens in the past and persistence of TCDD in the environment.

Is there a plausible alternative source of elevated TCDD in southern Vietnam? In this regard, it is of interest that the mean TCDD level in adipose tissue of 15 parts per trillion (ppt) in the southern samples is three times greater than the 5 ppt found in an epidemiologic study of samples in the United States.[2] The blood levels also exceed those reported for US samples by a factor of 3 (13 ppt vs 4 ppt).[3] Given the current theory that environmental TCDD results primarily from industrial processes,[4] it is difficult to identify plausible alternative sources of TCDD in the environment of southern Vietnam that would produce levels exceeding those in the US.

If we accept that there is some subpopulation in Vietnam with protracted exposure to TCDD, then the next important question concerns the evidence of adverse health effects of such exposure. More precisely, at what concentration of TCDD in blood or tissue does the risk of adverse effects increase and by how much? There is now a substantial body of animal and epidemiologic data that addresses this question, especially in the case of cancer outcomes.

Treatment with TCDD has been associated with increased neoplasms in every animal bioassay reported in the scientific literature.[5] These carcinogenicity models have included several species and tumors at multiple sites. Furthermore, carcinogenic effects occur at concentrations as low as 1.4 ng/kg per day. The carcinogenicity of TCDD has also been reported for the Syrian Hamster[6]—a finding of particular importance since hamsters, like humans, are relatively resistant to the acute toxic effects of TCDD.

**Editor's Note.** See related article by Schecter et al. (p 516) in this issue.